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Metabolic modelling of the human gut microbiome: framing the problem to use GAMA

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Abstract

The gut microbiome, a collection of microorganisms in the digestive tract, plays a crucial role in health by aiding nutrient digestion, shaping immune responses, and producing bioactive molecules that interact with the host. Advances in next-generation sequencing have revealed the vast diversity of microbial communities, showing individual-level genetic variability far exceeding the human genome.

In microbiome research, AI algorithms have identified biomarkers linked to clinical conditions, characterized ecosystem structures, and detected compositional shifts in response to environmental or nutritional changes. However, most biomarkers lack biological explanations, particularly regarding microbiota responses to environmental shifts and their functional impacts on metabolite production and inter-species interactions. Thus, new analytical methods are needed to uncover the mechanisms behind microbiome composition changes, which could guide strategies to manipulate the microbiome for improved health.

In this context, a systemic approach based on modeling different types of molecular networks (metabolic, regulatory, protein-protein interaction) that integrate quantitative data from various Omics technologies could contribute to a mechanistic understanding of the functional capacities of the intestinal microbiome and its potential interactions with the human host. These interactions can be computationally modeled through the reconstruction of cellular metabolic networks, which can range from a set of organisms (specific bacteria of interest, for example, probiotic bacteria) to the entire functional activities of the community, independent of cellular boundaries. At computational level, modelling approaches developed to study the gut microbiome metabolism ranges from metabolite-agnostic approaches that describes changes in species abundances over time as function of growth rates and pairwise interactions to metabolite-explicit modelling approaches that exploit the network of biochemical transformations happening in the gut ecosystem at different levels of complexity, allowing to link specific gut microorganisms to changes in metabolite concentrations found in the interplay with nutrition and clinical host conditions. In this approach, the key element is the coupling of Genome-Scale metabolic models (GSMM) of individual microorganisms with mathematical optimization methods such as linear programming, which allows for the determination of the distribution of metabolic fluxes through the model's reactions that maximize individual and community biomass. In this presentation we will show how different modelling approaches have been applied to study the gut microbiome in the interplay between nutrition and human health to open a discussion on how an agent-based approach, such as the one provided by GAMA, could complement these modeling techniques by representing individual microorganisms as agents, each with distinct characteristics and behaviors. In this framework, agents would interact with each other and the environment (i.e., the host's gut ecosystem), allowing for the simulation of complex biological processes and dynamic interactions within the microbiome. GAMA could be used to model not only microbial growth and metabolic interactions but also the spatial organization of bacteria, how they compete or cooperate, and how external factors like diet, medication, or environmental changes influence these interactions. By integrating agent-based models with GSMM and multi-omics data, this approach could offer a more comprehensive representation of the gut microbiome, accounting for both mechanistic insights at the cellular level and emergent behaviors at the community level.

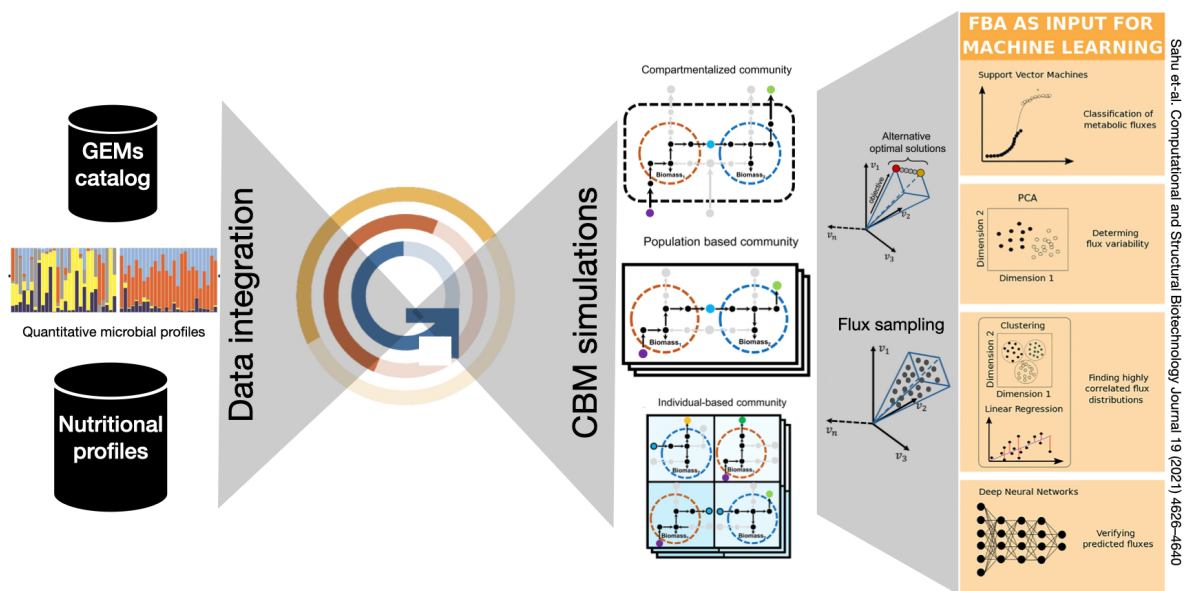


Figure 1: Metabolic modelling of the human gut microbiome: framing the problem to use GAMA